AGA Clinical Practice Update on the Evaluation and Management of Acute Kidney Injury in Patients With Cirrhosis: Expert Review

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DESCRIPTION: **The purpose of this American Gastroenterological Association (AGA) Institute Clinical Practice Update is to review the available published evidence and expert advice regarding the clinical management of patients with suspected acute kidney injury in patients with cirrhosis.**

METHODS: **This article provides practical advice for the management of patients with cirrhosis and acute kidney injury based on the best available published evidence. This best practice document is not based on a formal systematic review. This expert review was commissioned and approved by the AGA Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through the standard procedures of *Clinical Gastroenterology & Hepatology*. These Best Practice Advice (BPA) statements were drawn from a review of the published literature and from expert opinion. Since systematic reviews were not performed, these BPA statements do not carry formal ratings of the quality of evidence or strength of the presented considerations.**

BEST PRACTICE ADVICE 1: **Acute kidney injury (AKI) should be diagnosed when the serum creatinine increases by ≥0.3 mg/dL within 48 hours or is ≥50% from baseline or when the urine output is reduced below 0.5 mL/kg/h for >6 hours.**

BEST PRACTICE ADVICE 2: **Preventive measures against the development of AKI in cirrhosis include (1) avoidance of potentially nephrotoxic medications like nonsteroidal anti-inflammatory drugs (NSAIDs), (2) avoidance of excessive or unmonitored diuretics or nonselective beta-blockade, (3) avoidance of large-volume paracentesis without albumin replacement, and (4) counseling patients to avoid alcohol use.**

BEST PRACTICE ADVICE 3: **(A) Investigation is directed to determining the cause of AKI, which can be due to hypovolemic causes (volume responsive, and the most common cause of AKI in patients with cirrhosis); acute tubular necrosis; hepatorenal syndrome with AKI (HRS-AKI) (a functional renal failure that persists despite volume repletion); HRS with acute kidney disease, a type of functional renal failure of <3 months– duration in which criteria for HRS-AKI are not met; or postrenal, which occurs only rarely. (B) The specific type of AKI should be identified through a careful history, physical examination, blood biochemistry, urine microscopic examination, urine chemistry (Na^+ and urea) and selected urinary biomarkers, and renal ultrasound.**

BEST PRACTICE ADVICE 4: **A rigorous search for infection is required in all patients with AKI. A diagnostic paracentesis should be carried out to evaluate for spontaneous bacterial peritonitis; blood and urine cultures and chest radiograph are also required. There is no role for routine prophylactic antibiotics in patients with AKI, but broad-spectrum antibiotics should be started whenever infection is strongly suspected.**

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BEST PRACTICE ADVICE 5: When AKI is diagnosed, diuretics and nonselective beta-blockers should be held, NSAIDs discontinued, the precipitating cause of AKI treated, and fluid losses replaced, administering albumin 1 g/kg/d for 2 days if the serum creatinine shows doubling from baseline. Urine output, vital signs, and when indicated, echocardiography or CVP (if there is a pre-existing central line) should be used to monitor fluid status.

BEST PRACTICE ADVICE 6: When the serum creatinine remains higher than twice the baseline value despite these measures, treatment of HRS-AKI should be initiated with albumin at a dose of 1 g/kg intravenously on day 1 followed by 20–40 g daily along with vasoactive agents (terlipressin; if terlipressin is not available, either a combination of octreotide and midodrine; or norepinephrine, depending on institutional preferences) and continued either until 24 hours following the return of the serum creatinine level to within ≤0.3 mg/dL of baseline for 2 consecutive days or for a total of 14 days of therapy.

BEST PRACTICE ADVICE 7: Terlipressin should be initiated as a bolus dose of 1 mg every 4–6 hours (total 4–6 mg/d). The dose should be increased to a maximum of 2 mg every 4–6 hours (total 8–12 mg/d) if there is no reduction in serum creatinine at day 3 of therapy by at least 25% compared to the baseline value. Alternatively, clinicians can administer terlipressin by continuous intravenous infusion at a lower starting dose of 2 mg/d, which may reduce ischemic side effects and increase the dose gradually every 24–48 hours up to a maximum dose of 12 mg/d, or reversal of HRS. As per Food and Drug Administration restrictions, terlipressin should not be used in patients with a serum creatinine ≥5 mg/dL, or oxygen saturation of <90%.

BEST PRACTICE ADVICE 8: Oral midodrine when used should be initiated at doses of 7.5 mg and titrated upward to 12.5 mg 3 times daily with octreotide (starting with 100 μg and titrating upward to 200 μg subcutaneously 3 times daily).

BEST PRACTICE ADVICE 9: Norepinephrine should be used as a continuous intravenous infusion at a starting dose of 0.5 mg/h and the dose increased every 4 hours by 0.5 mg/h to a maximum of 3 mg/h with the goal of increasing the mean arterial pressure by ≥10 mm Hg and/or the urine output to >50 mL/h for at least 4 hours.

BEST PRACTICE ADVICE 10: The risks of ischemic side effects of terlipressin and norepinephrine include angina and ischemia of fingers, skin, and intestine. These side effects may be lowered by starting at the lowest dose and gradually titrating upward.

BEST PRACTICE ADVICE 11: Fluid status should be closely monitored because of the risk of pulmonary edema with excessive use of albumin.

BEST PRACTICE ADVICE 12: Renal replacement therapy (RRT) may be used in the management of (A) AKI secondary to acute tubular necrosis; (B) HRS-AKI in potential candidates for liver transplantation (that is, RRT should not be used in patients with HRS-AKI who are not candidates for liver transplantation); and (C) AKI of uncertain etiology in which the need for RRT may be considered on an individual basis.

BEST PRACTICE ADVICE 13: Transjugular intrahepatic portosystemic shunts should not be used as a specific treatment of HRS-AKI.

BEST PRACTICE ADVICE 14: Liver transplantation is the most effective treatment for HRS-AKI. Pharmacotherapy for HRS-AKI before proceeding with liver transplantation may be associated with better post-liver transplantation outcomes. Selected patients with HRS-AKI may require simultaneous liver kidney transplantation based on updated Organ Procurement and Transplantation Network listing criteria.

Acute kidney injury (AKI) occurs in 47% of patients hospitalized with complications of cirrhosis[1] and in about 30% of outpatients with cirrhosis,[2] with $4 billion in total hospitalization costs in the United States.[3] AKI in patients with cirrhosis is associated with a 7-fold increase in morbidity and mortality vs those without AKI.[4] Repeated episodes of AKI increase the risk of progression to chronic kidney disease (CKD).[5]

AKI has traditionally been defined by an increase in serum creatinine. The assay for serum creatinine is widely available

Table 1. Comparison of Previous and Current HRS Diagnostic Criteria

HRS Type 1 (Previous)	HRS-AKI (Current)
• Doubling of serum creatinine within 2 wk to a level >2.5 mg/dL • Lack of response to diuretic withdrawal and 2-d volume challenge with albumin 20%–25% in a dose of 1 g/kg/d • Cirrhosis with ascites • Absence of shock • No current or recent use of nephrotoxic drugs (NSAIDs, contrast dye, etc.) • No signs of structural kidney injury ◦ Absence of proteinuria (>500 mg/d) ◦ Absence of hematuria (>50 RBCs per high-power field) ◦ Normal findings on renal ultrasound	Increase in serum creatinine ≥0.3 mg/dL within 48 h OR Increase in serum creatinine ≥1.5 times (>50% increase) from baseline within 7 d (use creatinine value within the previous 3 mo that is closest to presentation as baseline value) • Lack of response to diuretic withdrawal and 2-d volume challenge with albumin 20%–25% in a dose of 1 g/kg/d • Cirrhosis with ascites • Absence of shock • No current or recent use of nephrotoxic drugs (NSAIDs, contrast dye, etc.) • No signs of structural kidney injury ◦ Absence of proteinuria (>500 mg/d) ◦ Absence of hematuria (>50 RBCs per high-power field) ◦ Normal findings on renal ultrasound
HRS Type 2 (Previous)	**HRS-NAKI (Current)**
• Gradual increase in serum creatinine to a level >1.5 mg/dL, not meeting previous criteria	b) HRS-AKD • Estimated glomerular filtration rate <60 mL/min/1.73 m2 for <3 mo in the absence of other potential causes of kidney disease. • Increase in serum creatinine ≥1.5 times (>50% increase) from baseline within 3 months (use creatinine value within the previous 3 mo that is closest to presentation as baseline value) b) HRS-CKD • Estimated glomerular filtration rate <60 mL/min/1.73 m2 for ≥3 mo in the absence of other potential causes of kidney disease

AKD, acute kidney disease; AKI, acute kidney injury; CKD, chronic kidney disease; HRS, hepatorenal syndrome; NAKI, nonacute kidney injury; NSAID, nonsteroidal anti-inflammatory drug; RBC, red blood cell.

and inexpensive but may underestimate the severity of reduction in renal function in patients with cirrhosis because of impaired hepatic production of creatine, the precursor of creatinine. Reduced muscle mass, female sex, and renal tubular secretion of creatinine also result in lower serum creatinine. Hyperbilirubinemia results in inaccurate measurement of serum creatinine by calorimetric methods. Nonetheless, the most common measures of renal function are serum creatinine and urine output. As per the Kidney Disease: Improving Global Outcomes organization clinical practice guidelines, AKI is defined by either an increase in serum creatinine by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 hours, an increase in serum creatinine to ≥1.5-fold from baseline that presumably has occurred within the previous 7 days, or urine volume <0.5 mL/kg/h for 6 hours.[6] The most recent serum creatinine value obtained within the previous 3 months is used as baseline when a value within the previous 7 days is not available. Though lower urine output can result from avid sodium and water retention that is associated with cirrhosis, reduction in urine output to <0.5 mL/kg for >6 hours is associated with higher mortality when compared with patients meeting only the creatinine criteria of AKI.[7] The Kidney Disease: Improving Global Outcomes diagnostic criteria identify patients at risk of longer hospital stay, multiorgan failure, and in-hospital and 30-day mortality.[8,9]

Types of AKI in Patients with Cirrhosis

The underlying pathophysiology common to renal complications of cirrhosis is a decrease in the effective arterial blood volume resulting from splanchnic vasodilatation.[10] Systemic vasoconstrictor pathways such as the renin-angiotensin-aldosterone system, the sympathetic nervous system, and arginine vasopressin are activated to increase the effective arterial blood volume.

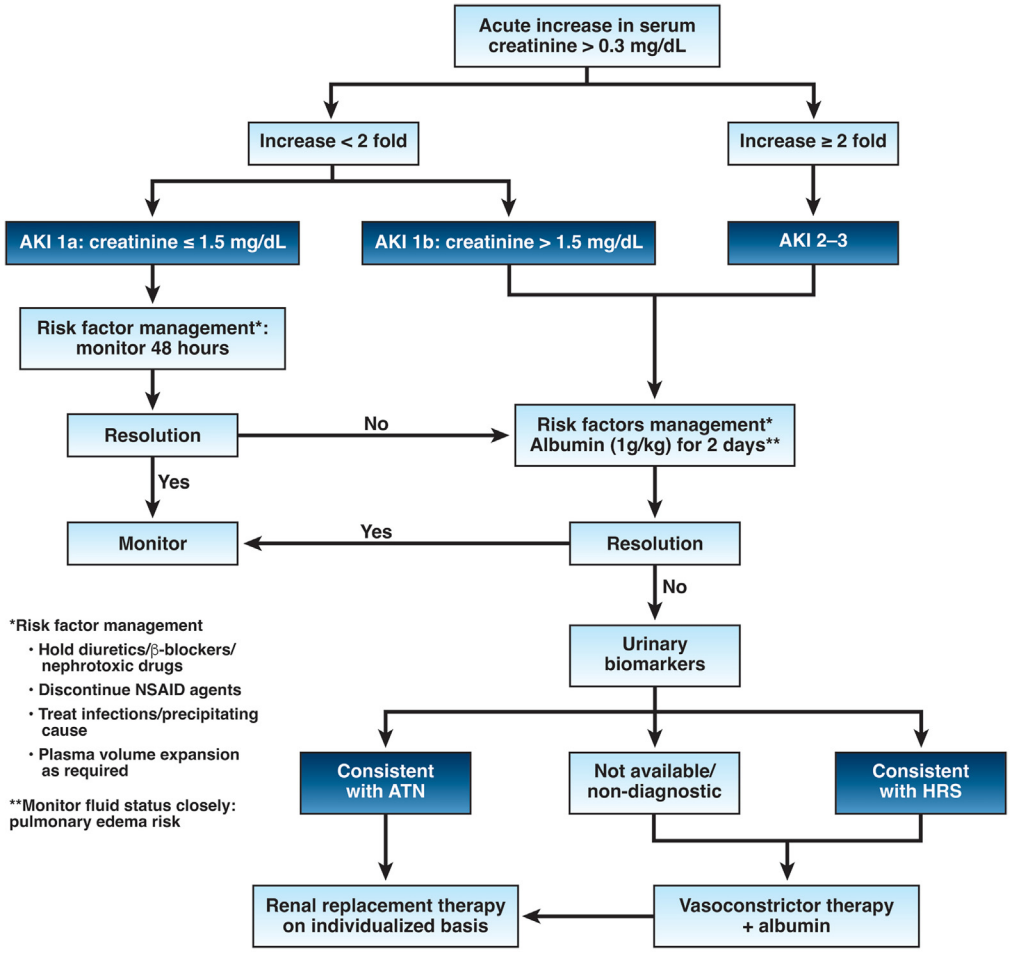

Figure 1. Algorithmic approach to management of AKI in patients with cirrhosis. Initial management of AKI (increase in serum creatinine >0.3 mg/dL in 48 hours) is geared toward reversing risk factors. In patients with stage 1 AKI (increase in serum creatinine >0.3 mg/dL but to <2 times baseline value), vasoconstrictor agents are not currently indicated but may be evolving. When the serum creatinine has increased > 1.5mg/dL (Stage 1b), or to ≥2 times baseline value (stage 2; or stage 3 is when serum creatinine has increased >3 times baseline value) and remains above these levels despite risk factor management for 2 days, then vasoconstrictor agents are indicated provided patient meets HRS criteria (Table 1). The indications for RRT are also outlined. Complete response to therapy is defined as return of the serum creatinine with treatment to <0.3 mg above baseline value; partial response is defined as reduction in serum creatinine but to >0.3 mg above baseline value. *Risk factor management involves holding diuretics, beta-blockers, and nephrotoxic drugs and discontinuing nonsteroidal anti-inflammatory drug [NSAID] agents); treating infections and other precipitating causes; and expanding plasma volume as required. **Careful monitoring for fluid overload is required when albumin is administered in patients with AKI because of the risk of pulmonary edema.

The result is renal sodium retention, impaired solute-free water excretion, and renal vasoconstriction that leads to reduced kidney blood flow and impaired function.

AKI in patients with cirrhosis may be due to hypovolemia, hepatorenal syndrome (HRS), or acute tubular necrosis (ATN). HRS, the most extreme manifestation of renal impairment, is characterized by a marked reduction in glomerular filtration rate (GFR) due to intense renal arteriolar vasoconstriction. Systemic inflammation, adrenal dysfunction, intra-abdominal hypertension, and the hepatorenal reflex also contribute to functional kidney injury. Hematuria and proteinuria are absent, urine sediment is usually normal, and the kidney appears normal on ultrasonography in HRS. Renal function may return to normal with the administration of pharmacological therapy or following liver transplantation (LT). Even though absence of renal damage is a criterion for diagnosis of HRS, tubular injury may be present on kidney biopsy.

Depending on the severity and duration of kidney injury, 2 forms of HRS are recognized: HRS-AKI, which represents acute impairment in renal function, and HRS–non-AKI, when patients with cirrhosis have functional kidney injury for >7 days in the absence of other causes of kidney disease (Table 1). This review provides supporting evidence that informs Best Practices Advice for management AKI in patients with cirrhosis.

Management of HRS-AKI

Prevention

HRS-AKI is often triggered by events that are potentially preventable.[10] Prevention measures include avoidance of alcohol use, monitoring of serum creatinine and electrolytes when patients are on diuretics, albumin infusion with therapeutic paracentesis, administering antibiotics with episodes of gastrointestinal bleeding, antibiotic prophylaxis against spontaneous bacterial peritonitis, and avoiding use of nonselective beta-blockers and nephrotoxic medications such as angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, and nonsteroidal anti-inflammatory drugs.[11,12]

It is unclear whether long-term albumin infusion prevents HRS. Long-term albumin administration reduced the likelihood of developing HRS and improved 18-month survival in one study,[13] but the results were not replicated in another study.[14] Patients may derive most benefit when the serum albumin is kept above 4 g/dL.[15] Albumin infusion may be associated with volume overload and life-threatening pulmonary edema.[16]

Initial Evaluation

In patients with AKI and cirrhosis, enquiry regarding use of nephrotoxic drugs, nonselective beta-blocker, radiographic contrast agents, diuretics, lactulose, excess alcohol use, infection and symptoms of vomiting, diarrhea, hematemesis, and melena is mandatory. Examination is geared toward detecting infection, assessing volume status, and monitoring for hepatic and extrahepatic organ failure.

Once the diagnosis of AKI is established, the etiology of the AKI, be it hypovolemic AKI (prerenal azotemia), ATN, or HRS-AKI, is determined. To exclude structural renal diseases, urinalysis is carried out to detect hematuria, proteinuria, or abnormal urinary sediment.[10] All diuretics should be withdrawn, and lactulose dosage adjusted to reduce severity of diarrhea. A fluid challenge using albumin at a dose of 1 g per kilogram of body weight to a maximum of 100 g/d should be administered.[17] Patients who have had significant blood loss should be given red cell transfusions to maintain a hemoglobin $\geq$8 g/dL, although volume status must be monitored carefully, and overtransfusion should be avoided. In hypovolemic AKI, volume replacement should be associated with a reduction in the serum creatinine to $\leq$0.3 mg/dL of the baseline level.

Investigations and interpretation. Patients with HRS-AKI have bland urine microscopic examination but do not respond with return of serum creatinine to $\leq$0.3mg/dL of baseline to fluid challenge alone. Infection should be ruled out by careful physical examination for evidence of cellulitis and pneumonia and by investigations including chest radiography, urine and blood cultures, and diagnostic paracentesis for exclusion of spontaneous bacterial peritonitis, the most common cause of HRS-AKI. Serum creatinine is measured daily to assess AKI stage. Small echogenic kidneys on ultrasonography indicate structural renal disease, but a pelvic ultrasound is usually not needed, as postrenal obstruction is an uncommon cause of AKI in patients with cirrhosis. Empirical antibiotic treatment is started before culture, and results are available only when infection is strongly suspected.

Urinary sodium and urea excretion. Urine sodium excretion in patients with HRS is usually <10 mEq/L but may be higher in patients who have recently received diuretics. The fractional excretion of sodium (FENa) reflects sodium handling more accurately than does urinary sodium alone but is affected by water reabsorption. FENa is used in the assessment of patients with low urine output: low FENa usually indicates volume depletion, whereas high FENa suggests renal sodium wasting as occurs in ATN. A FENa cutoff of <1% suggests prerenal causes including HRS, and FENa >1% is suggestive of structural causes of AKI like ATN. However, a recent study assessing patients on a liver transplant waiting list reported no correlation between the FENa and the etiology of AKI on kidney biopsy. In fact, in cirrhosis, an FENa of <1% had a sensitivity of 100% but a specificity of only 14% in diagnosis of prerenal causes of AKI.[18] Fractional excretion of urea (FEUrea) may better discriminate HRS from prerenal azotemia or ATN. Urea, mainly reabsorbed in the proximal renal tubule and collecting ducts, is not modified by diuretic use. In a small retrospective study, FEUrea of <28.16% had a sensitivity of 75% and specificity of 83% in separating HRS from non-HRS.[19] Therefore, FEUrea may be used in the differential diagnosis of HRS-AKI.

Other serum and urinary biomarkers. Biomarkers may be used to estimate GFR and to differentiate structural vs functional renal diseases. Cystatin C, a low-molecular-weight protein produced by all nucleated cells, is usually removed by glomerular filtration. Serum cystatin C levels represent a more accurate estimation of GFR and are less influenced by age and diabetes than is serum creatinine; decreased GFR is associated with higher levels of cystatin C. A recent meta-analysis found that the combination of serum cystatin C and creatinine has the least bias in the estimation of GFR in cirrhosis.[20] However, the meta-analysis included only a few studies in patients with ascites or on the liver transplant waiting list[21]; therefore, the results may not be applicable to most patients at risk for the development of HRS.

Biomarkers of renal tubular injury include tubular proteins released during cell damage (N-acetyl-β-D-glucosaminidase, α-glutathione S-transferase) or tubular proteins upregulated by injury such as KIM-1 (kidney injury molecule 1), and neutrophil gelatinase–associated lipocalin (NGAL). Markers of inflammation such as interleukin-18 and plasma proteins that have reduced tubular

reabsorption because of renal tubular cell damage have also been used (α1-microglobulin, β2-microglobulin, retinol binding protein).[22,23] In general, the more biomarkers that are elevated, the more likely it is that the patient has ATN.[24] NGAL is the most studied biomarker, and urinary NGAL performs better than serum NGAL when measured 2 days following a fluid challenge. The level of NGAL in patients with HRS-AKI is always much lower than that in patients with ATN, even if the HRS-AKI has not responded to treatment.[25] A cutoff value of 220–244 μg/g of creatinine has been reported as best for differentiating ATN from prerenal azotemia or HRS and may predict 90-day mortality,[26,27] but NGAL measurements are not widely available in the United States for clinical use.

Pharmacological Treatment of HRS-AKI

Albumin. Albumin is used in the management of HRS-AKI because of its volume-expanding, anti-inflammatory, and other non–oncotic-related properties. An intravenous albumin challenge of 1 g per kilogram of body weight per day for 2 consecutive days without demonstrated improvement in serum creatinine in patients meeting other criteria outlined in Table 1, confirms the diagnosis of HRS-AKI. Albumin as therapy for HRS-AKI is administered in a dose of 20–40 g/d together with vasoconstrictors.[28] If albumin is unavailable, crystalloids can be administered. However, albumin is the optimal therapy, as it is more effective than crystalloids for treatment of HRS-AKI. Albumin alone is ineffective in the management of HRS-AKI.[29,30] Though higher total doses of albumin may be associated with improved 180-day survival,[31] excessive albumin may lead to respiratory failure.[29] Therefore, albumin use in the context of HRS requires careful monitoring to avoid volume overload.

Vasoconstrictors. Splanchnic vasoconstrictors, the mainstay of pharmacological treatment for HRS-AKI, are used to reverse the splanchnic vasodilatation responsible for the development of HRS. Vasoconstrictor therapy should be started as soon as possible, as higher pretreatment serum creatinine is associated with treatment failure (Figure 1). Even small reductions in serum creatinine with treatment are beneficial, and every 1-mg/dL drop in serum creatinine is associated with a 27% reduction in the relative risk for mortality.[32] The vasoconstrictor agents used are terlipressin, a vasopressin analog; norepinephrine and midodrine, both α-1 adrenergic receptor agonists acting directly on the vascular smooth muscle cells; and octreotide, a somatostatin analog that acts as an inhibitor of glucagon, a splanchnic vasodilator. Octreotide also has direct splanchnic vasoconstrictive effect. To date, all the studies published have mainly assessed patients diagnosed according to the previous definition of type 1 HRS.

First, for terlipressin, there have been 4 randomized controlled trials, 1 in Europe and 3 in North America, totaling 646 patients, comparing the efficacy of terlipressin combined with albumin vs placebo with albumin in reversing HRS.[29,33–35] The response rate varied between 36% and 44%, possibly related to the differences in the populations of patients studied, dosing regimens, or duration of treatment. Approximately 25% of patients included in the European study were diagnosed with the previous definition of type 2 HRS. There was no difference in the overall survival or transplant-free survival between the terlipressin and placebo groups. In the most recent study carried out in the United States and Canada, 29% of patients reversed their HRS and survived for an additional 10 days after completion of treatment without the need for renal replacement therapy (RRT).[29] This small extension in survival may allow time for patients to receive a liver transplant.

Patients on terlipressin need to be monitored for the development of ischemic complications such as arrhythmia, angina, and splanchnic and digital ischemia. Terlipressin should not be resumed in patients who experience cardiac or ischemic symptoms, even if the symptoms have subsided following discontinuation of treatment. In the Multi-Center, Randomized, Placebo Controlled, Double-Blind Study to Confirm Efficacy and Safety of Terlipressin in Subjects With Hepatorenal Syndrome Type 1 (CONFIRM study for HRS-1),[29] 30% patients in the terlipressin arm experienced respiratory failure, especially in patients with another concomitant organ failure.[36] Respiratory failure was associated with a higher international normalized ratio, mean arterial pressure (MAP), and oxygen saturation at baseline.[36] Therefore, clinicians should exercise extra caution when terlipressin is administered to such patients.

Terlipressin is usually administered as intravenous bolus doses at 1–2 mg every 6 hours for up to 14 days but is discontinued if there is no response on day 3 or 4. Continuous infusion of terlipressin has similar efficacy with lower total daily dose and fewer side effects.[37] Predictors of response to terlipressin include a baseline bilirubin of $<$10 mg/dL, a baseline serum creatinine of $<$5 mg/dL, and lower stage of acute-on-chronic liver failure.[38–40] A sustained increase in MAP by 5–10 mm Hg with treatment is associated with response to terlipressin.[30] Patients with systemic inflammatory response syndrome, alcohol-associated hepatitis, and sepsis may respond better than patients without these factors.[29,41–43]

Second, the randomized controlled trials studying norepinephrine as a treatment for HRS have used terlipressin in the control arm. All the trials were small, totaling 96 patients in the terlipressin arm and 99 patients in the norepinephrine arm.[44–48] Norepinephrine was administered at a dose 0.5–3 mg/h and adjusted to increase MAP $\geq$10 mm Hg. Norepinephrine improved renal function in 39%–70% of patients, similar to that observed in the terlipressin arm. However, in the setting of acute-on-chronic liver failure (as defined by serum bilirubin $>$5 mg/dL and international normalized ratio $>$1.5 together with the onset of either hepatic

encephalopathy or ascites within 4 weeks), terlipressin was superior to norepinephrine.[49]

Norepinephrine is administered in a starting dose of 0.5 mg/h and the dose increased every 4 hours by 0.5 mg/h to a maximum of 3 mg/h with the goal of increasing the MAP ≥10 mm Hg or the urine output to >50 mL/h for at least 4 hours. Because norepinephrine must be administered in a monitored setting in the intensive care unit (ICU), this adds significantly to the cost of using norepinephrine, which by itself is a relatively inexpensive drug. In a small feasibility study, norepinephrine infusion outside the ICU was found to be safe.[50] However, ischemic complications, cardiac arrhythmias, and respiratory side effects may occur.

Third, the combination of midodrine and octreotide is widely used in North America because until very recently terlipressin was not available, and norepinephrine must be administered in the ICU. The combination of midodrine and octreotide works very slowly, but reversal of HRS is possible. Octreotide alone is ineffective, as its splanchnic vasoconstrictive effect is largely counteracted by the large number of vasodilators in the splanchnic circulation. The combination of midodrine and octreotide is inferior to terlipressin in improving renal function or HRS reversal.[51] Midodrine and octreotide are generally well tolerated. Headaches, blurred vision, cardiac palpitations, and rash may be observed with midodrine. Fatigue, nausea, emesis, abdominal pain, or back pain may occur with octreotide.

Indications for dialysis. In general, RRT in patients with HRS-AKI unresponsive to pharmacologic therapy is indicated only as a bridge to LT for current candidates or patients who may become candidates to treat volume overload, electrolyte derangements, or uremia.[52] However, in such patients, prognosis is still guarded, with mortality of 59% in patients requiring >7 days of RRT.[53] Continuous RRT is preferred, as it results in lower fluid shifts and reduced hemodynamic instability when compared with intermittent RRT.[54] Two-thirds of patients with HRS-AKI undergoing RRT pretransplantation recover renal function when they receive a liver transplant.[55,56] The cutoff duration of RRT for predicting renal function recovery is approximately 14 days.[55,56] For every additional day dialysis pretransplantation, there is a 3.6%–6% increased risk for renal nonrecovery post-transplantation[56,57] and a greater need for kidney transplantation.

RRT is also indicated in patients with all etiologies of AKI if they are candidates for LT or if they may become candidates for LT. In patients who are not candidates for LT, RRT is indicated if they have ATN, and, at least for a limited period, when the etiology of AKI is uncertain.[58]

Transjugular intrahepatic portosystemic shunts. Transjugular intrahepatic portosystemic shunts cannot currently be advised for the specific treatment of HRS-AKI in the absence of data supporting their use.

Liver transplantation. LT is the optimal treatment for HRS-AKI because liver failure underlies the development of HRS-AKI and is generally reversible with LT. Because many patients have contraindications for LT, and donor organs are limited, patients with HRS-AKI may die while awaiting LT. Moreover, patients with HRS-AKI have worse pre-LT prognosis than patients with other causes of AKI, but etiology of AKI is not accounted for in liver allocation prioritization in the Model for End-Stage Liver Disease (MELD) sodium–based system.[59,60]

There is concern that reversal of HRS-AKI with pharmacological therapy lowers the serum creatinine with resulting decrease in the Model for End-Stage Liver Disease (MELD) sodium score, thereby reducing prioritization for LT. Nevertheless, medical treatment should not be withheld in such patients, as the benefits of effective management outweigh the potentially deleterious consequences of decreased priority for liver allocation. The duration of kidney injury and the presence of ATN impacts the likelihood of renal recovery.[61] Post-LT renal insufficiency and ongoing requirement of RRT are correlated with decreased post-transplantation survival.[62,63] On the other hand, improved renal function may be associated with improved survival. Terlipressin with albumin has been shown to decrease requirement of LT, improve 30-day pretransplantation survival, and lower risk of chronic renal disease after LT,[64] but another study could not confirm these results.[65] Despite the conflicting data, expert opinion indicates that patients with HRS should be treated prior to LT because it may improve post-transplantation outcomes.[11,12]

Although renal function recovers after LT, improvement is not universal.[66] In fact, approximately 25% of patients remain dialysis dependent after LT,[67,68] especially if they are younger, have chronic renal disease, and require RRT prior to transplantation. Other studies, however, did not confirm that pretransplantation RRT predicted post-transplantation renal insufficiency and mortality.[69,70]

Selected patients with HRS-AKI may require simultaneous liver-kidney transplantation based on updated Organ Procurement and Transplantation Network listing criteria. After implementation of the MELD scoring system for liver allocation in the United States in 2002, there was a >300% increase in the number of simultaneous liver-kidney transplantation procedures because renal dysfunction increases MELD score and priority for transplantation.[71,72] As a result, the Organ Procurement and Transplantation Network policy was implemented by United Network for Organ Sharing in 2017 to optimize usage of kidneys by allowing for improvement in native renal function after LT. Currently, simultaneous liver-kidney allocation candidacy requires that a patient be on dialysis or have a measured or calculated GFR ≤25 mL/min for ≥6 consecutive weeks.[73] Patients can be registered for renal transplantation alone with high priority if they have persistent renal dysfunction, defined by end-stage renal disease or GFR <20 mL/min after LT.[73]

Table 2. Future Directions in the Management of AKI

1. Prevention of and protection against kidney injury: better definition of role of intravenous albumin and oral vasoconstrictors
2. Biomarkers for i. Early diagnosis of AKI independent of serum creatinine ii. Distinguishing between types of AKI without kidney biopsy iii. Predicting reversibility and irreversibility
3. Initiation and stopping rules for renal replacement therapy
4. Transplantation i. Maintaining priority for liver transplantation in patients who respond to pharmacological treatment of HRS-AKI ii. Markers to identify patients who require simultaneous liver kidney transplantation vs liver transplantation alone
5. Development and validation of patient-reported outcomes

AKI, acute kidney injury; HRS, hepatorenal syndrome.

Future Directions

AKI has a negative impact on survival; therefore, measures are required to avoid situations that lead to kidney injury. The association between AKI and nephrotoxic drugs, large-volume paracentesis, and infection, etc. is recognized and has informed preventative measures and early diagnosis among expert clinicians. However, there is a paucity of studies that have systematically addressed how AKI in patients with cirrhosis can be prevented using these measures (Table 2). In addition to preventive strategies, kidney protective strategies need to be developed. The uncertain efficacy and costs and logistics involved make weekly albumin administration an unattractive kidney-protective approach. Orally administered drugs that can reverse the splanchnic vasodilatation and restore effective arterial blood volume need to be developed.

Current strategies to diagnose and monitor progression of AKI rely heavily on measurement of serum creatinine, which is not an ideal measure of glomerular filtration, especially in women and children. Accurate measures of glomerular filtration using iothalamate clearance are expensive and have limited availability. In addition, differentiation between HRS-AKI and ATN is difficult in many situations and may require a kidney biopsy. The strategy of kidney biopsy is also problematic given the risks, expense, and paucity of pathology expertise. Biomarkers such as NGAL may differentiate between HRS-AKI and ATN but are currently not available for clinical use. Therefore, there is the need for easily available biomarkers to diagnose and monitor the stage of AKI, differentiate between HRS-AKI and ATN, and determine whether the kidney dysfunction is reversible or not.

The role of RRT also needs to be better defined. Specifically, the type and duration of RRT need to be studied further such that rules for initiation of RRT as well as discontinuation of RRT can be developed.

Hyponatremia is almost universal in patients with HRS-AKI, but optimal treatment measures are yet unclear and need to be defined.

LT is the definitive treatment for HRS-AKI, but it is yet unclear which patient benefits from LT alone and in whom a simultaneous liver-kidney transplantation should be carried out. Moreover, the current MELD-based allocation system for LT lowers priority for LT for patients with HRS-AKI who respond to pharmacological treatment, suggesting the need to maintain a high priority for LT for patients with HRS-AKI even if they have responded to therapy with lowering of the serum creatinine.

Currently, all treatment decisions regarding AKI in patients with cirrhosis are based either on survival or on investigator-initiated endpoints. No studies have been conducted using patient-reported outcomes, an endpoint increasingly being required by regulatory bodies. Therefore, the need to develop patient-reported outcomes in patients with cirrhosis with AKI is an important future initiative.

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